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Piper Marbury Rudnick & Wolfe
P.O. Box 64807
Chicago, IL 60664-0807

EXAMINER
KALLIS, RUSSELL

ART UNIT	PAPER NUMBER
1638	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/779,237	Applicant(s) BOTHA ET AL.	
	Examiner Russell Kallis	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received

2.☐ Certified copies of the priority documents have been received in Application No. _____

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Sequence Rules

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth:

> § 1.821 Nucleotide and/or amino acid sequence disclosures in patent applications;
>
> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Applicant must amend the claims, specification, and/or drawings to insert sequence identifiers.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 1-6, 8-14, and 17-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn toward the isolated nucleotide sequence of SEQ ID NO: 1, an untranslatable form thereof, an antisense form, a sequence that is complementary to, fragments, portions, and variants of, as well as sequences that hybridize, under stringent conditions, to the nucleotide sequence of SEQ ID NO: 1, plants transformed with sequences thereof, and methods of manipulating active PFP-β polypeptide and sucrose in transformed plants.

Applicant describes the PFP nucleotide sequence of SEQ ID NO: 1 and transformation vectors pUSPc510 and pASPc510.

Applicant does not describe the composition or structure of any of the claimed sequences other than the sequence of SEQ ID NO: 1. Therefore, it is not clear that Applicant was in possession of the invention as broadly claimed.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The court also addressed the manner by which genus of cDNAs might be described: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.* At 1406.

4. Claims 5, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that pUSPc510 and pASPc510 are required to practice the claimed invention. The specification does not provide a repeatable method for obtaining and it does not appear to be readily available material. Without a publicly available deposit of the above, one of ordinary skill in the art could not be assured of the ability to make sugarcane with down regulated PFP activity in the same manner as claimed. Given the lack of guidance in the specification and inability of those in the art to reproduce specific plant expression vectors, it would require undue experimentation for one skilled in the art to identify and obtain the original vector and the polynucleotide encoding the PFP enzyme from sugarcane. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of pUSPc510 and pASPc510. See 37 CFR 1.802.

Deposit of plant expression vectors pUSPc510 and pASPc510 would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be

irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

(a) during the pendency of this application, access to the deposits will be afforded to one determined by the commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in the public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposits will be replaced if they should become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.801 - 1.809 [MPEP 2401-2411.05] for additional explanation of these requirements.

5. Claims 1-6, 8-14, and 17-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is enabling only for claims limited to the isolated sugarcane PFP nucleotide sequences of SEQ ID NO: 1 and SEQ ID NO: 2, a method of down regulating the total activity of the PFP enzyme in a plant by transformation with a plant expression vector comprising either a sense or an antisense version of SEQ ID NO: 2 encoding the PFP-β subunit from sugarcane such that sucrose content is increased. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant claims a method of regulating and manipulating sucrose content in a sugar storing plant by regulating the activity of the PFP enzyme in the plant by transformation with a plant expression vector comprising either an untranslatable sense or an antisense polynucleotide or fragment thereof encoding a PFP enzyme subunit such that sucrose content is increased.

Applicant teaches cloning and characterization of a full length sugarcane PFP-β cDNA of SEQ ID NO: 2 using degenerate PCR primers based upon the castor bean and potato sequences for PFP-β to make a sugarcane probe to probe a sugarcane cDNA library (page 7, lines 13-24), construction of plant expression vectors comprising an untranslatable sense or antisense version of SEQ ID NO: 1, (a 1170 b.p. fragment of SEQ ID NO: 2), the maize polyubiquitin UBI promoter, and the CaMV 35S promoter (page 8, lines 5-18), and transformation and identification by PCR analysis of sugarcane transformed with a vector comprising the sense construct PFP-β (page 8, lines 20-33, page 9, lines 1-16). Applicant teaches that the transformed plants have decreased total activity of the PFP enzyme and sucrose content is increased (page 10, Table 1).

Applicant does not teach the cloning and characterization of PFP cDNA, fragments, variants from sugar storing plants other than sugarcane, the construction of plant expression vectors that comprise PFP cDNA fragments or variants from other sugar storing plants, transformation of sugar storing plants, or down regulation of the total activity of the PFP enzyme in sugar storing plants by transformation with a plant expression vector comprising either an untranslatable sense or an antisense polynucleotide encoding the PFP subunit from a target plant other than sugarcane such that sucrose content is increased; or reasonably provide enablement for methods other than transformation with a plant expression vector comprising a sugarcane PFP in sense orientation, such as methods using chemicals other than DNA to affect sucrose metabolism, a method using PFP sequences from other species or DNA sequences other than PFP that could also down regulate expression of a PFP enzyme, or down regulation of PFP in other sugar storing plants. Furthermore, the specification does not reasonably provide enablement for portions or variants of sugarcane PFP cDNA or other PFP sequences from other species of plants.

The inherent unpredictability in isolation of a nucleotide sequence encoding PFP is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity and that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun *et al.* Science Vol. 282 13 November 1998; Abstract lines 4-6 and p. 1317 column 1, lines 51-56). Given that there is some degree of non specific binding in either PCR isolation of cDNA or probing cDNA libraries one of skill in

the art would be required to screen through false positives to isolate the number of cDNA clones from the myriad of species commensurate with these claims.

Antisense inhibition of gene expression in transgenic plants using partial gene fragments is highly unpredictable. For example, expression of three constructs from different sections of one cDNA resulted in tissue specific reduction and increases of cDNA expression that varied with both construct and insertion event (Genetic Manipulation of Condensed Tannins in Higher Plants by Robbins *et al.* Plant Physiol., 116: 1133-1144, 1998). The 3' half of an antisense cDNA construct was more effective than the 5' half in inhibition of flower pigmentation by antisense CHS genes (van der Krol *et al.*, Plant Molecular Biology, 14: 457-466, 1990). Further, when antisense fragments are small enough to comprise only a conserved motif or region of a gene, the antisense fragments can exert an antisense effect upon other expressed genes in the genome that have the same motif or region. Furthermore, variants of sense constructs were expected to co-suppress an endogenous nitrite reductase gene in transgenic tobacco but did not yield the expected phenotype (Vaucheret *et al.* Plant Mol Biol 1999 Sep; 41(1):105-14; Abstract, lines 1-7).

In view of the lack of guidance provided in the specification, one of skill in the art would be required to screen a multitude of sequences of various lengths and from different regions of the PFP gene and screen through countless transformants testing different sense variants and different lengths of antisense PFP sequences to determine which constructs would confer an increase in sucrose content by means of a reduction in the activity of PFP commensurate in scope with the claims.

Given the lack of guidance, the absence of working examples in the specification that reflect the breadth of the claims, and the unpredictability in the art, undue trail and error would be needed to practice the invention. Therefore, the invention is not enabled throughout the broad scope of the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-6, 8-15, and 17-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 1, lines 1 and 2, it is indefinite what is encompassed by "regulating and manipulating . . . the activity". It is unclear if the enzyme is to be up regulated or down regulated and if total or specific activity is to be regulated. Also, it is not clear how "regulating" differs from "manipulating".

At Claim 1, "by" should be --comprising-- to constitute a proper method claim.

At Claim 2, line 2, it is indefinite what is encompassed by "down regulation of the PFP enzyme". It is unclear if the total activity of the PFP enzyme is to be down regulated or if the specific activity is to be down regulated.

Claims 2-4 are improperly dependent upon the previous claims. It is not clear whether the single method step of Claim 1 "regulating" is further limited or if other method steps are added. Also all method steps should be in the present participle verb tense, e.g. "introducing".

Appropriate correction is required.

At Claim 6, line 6 (iii), it is indefinite what is meant by "a variant". It is unclear if the variant is to encompass nucleotide substitutions and to what extent, or if it encompasses the length of the polynucleotide.

At Claim 6, line 9, it is indefinite what is meant by "stringent hybridization conditions". "Stringent" is a relative term and hence it is not known what hybridization/wash conditions are intended, and what nucleotide sequences are encompassed by the claim.

At Claim 9, line 1, "nucleotide sequence" lacks an article.

At Claim 9, line 2, "a sense orientation" should be --the sense orientation--.

At Claims 10 and 11, it is unclear where the two promoters are located, i.e. whether they are in tandem or drive expression of separate genes. Also, it is not clear whether they are in addition to the promoter recited in Claim 9 or in place of.

At Claims 13 and 14, it is unclear where the two promoters are located, i.e. whether they are in tandem or drive expression of separate genes. Also, it is not clear whether they are in addition to the promoter recited in Claim 9 or in place of.

At Claim 18, "derived from" is indefinite. Since there are many types of derivitaves, it is unclear what is encompassed.

At Claim 19, "callus" is indefinite. Since callus is undifferentiated plant material it is not a plant part.

At Claims 20 and 21, line 2, "a lower level of the PFP β protein" is indefinite. It is unclear to what the PFP β protein level is compared.

At Claims 22 and 23, line 2, "a lower level of PFP activity" is indefinite. It is unclear to what the PFP activity is compared.

At Claims 24 and 25, "a higher level of sucrose" is indefinite. It is unclear to what the level of sucrose is compared.

At Claims 26, 27 and 28, "including" should be --comprising--.

At Claim 26, "a method of regulating or manipulating" is indefinite. It is unclear what is intended. In either case regulation or manipulation are both indefinite because it is not clear in what fashion the level of active PFP is to be regulated or manipulated. Also, it is unclear how "regulating" differs from "manipulating".

At Claim 27, "maintaining . . . the sucrose level" is indefinite. It is unclear what is intended. Since maintaining the sucrose level would appear to encompass no change in level, it is not clear how such plant tissue would be recognized.

At Claim 28, "co-transforming the cell" is indefinite. It is not clear what else the cell is transformed with other than the gene construct of Claim 9.

Claim 29 is improperly dependent. It is not clear how the single method step of "co-transforming the cell" is further limited.

At Claim 30, "the plant" lacks proper antecedent basis.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-4, 6, 8, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hajirezaei *et al.* (Planta 1994, 192:16-20).

The claims are indefinite for the reasons discussed supra. In particular, "variant" and "stringent hybridization conditions" are indefinite and hence the claims read on essentially any nucleotide sequence. Also, since all plants store some sugar, all plants can be considered "sugar storing plants", and hence the claims read on all plants.

Hajirezaei teaches an isolated nucleotide sequence encoding PFP, a method of down regulation of PFP activity and increasing the sucrose content in tobacco, a sugar storing plant, by transformation with a plant expression vector comprising an antisense PFP nucleotide sequence, and plant thereby transformed (Abstract lines 1-12, in Tables 10 and 11, page 17 column 2, lines 40- 51, and on page 25 column 1, lines 3-13). Thus, Hajirezaei discloses the limitations of instant claims 1-4, 6, 8, and 12.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-4, 6, 8-14, and 17-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hajirezaei *et al.* (Planta 1994, 192:16-20) in view of Tanzer *et al.* (The Plant Cell, Vol. 9, 1411-1423, August 1997), Cheng *et al.* (PNAS USA Vol. 95 pp. 2767-2772), and Applicant's admission.

The teachings of Hajirezaei are discussed supra. Hajirezaei also teaches that said plant expression vector is derived from pBIN19 (page 17 column 2, lines 43-46). It is well known in the art that pBIN19 comprises two promoters, one driving a kanamycin selectable marker gene

and one driving the heterologous gene. Hajirezaei also teaches said vector with the CaMV 35S promoter (page 17 column 2, lines 34-43).

Hajirezaei does not teach the use of an untranslatable sense construct to reduce PFP expression in plants and increase sucrose content in transgenic plants. Hajirezaei also does not teach transformation of sugarcane and Hajirezaei does not teach the use of a maize ubiquitin promoter.

Tanzer teaches expression of sense mRNA and sense mRNA modified to have nonsense codons for TEV coat protein, gives rise to TEV resistant tissues in transgenic plants (Abstract lines 1-3).

Cheng teaches expression of lepidopteran specific δ-endotoxins using the maize ubiquitin promoter, ranging from 0.0 to 3.0% of total soluble protein, (see Abstract lines 4-12; figure 1, page 2768; and page 2769 column 2, lines 3-14).

Applicant admits that methods of sugarcane transformation were known at the time of Applicants invention (specification, p. 8, lines 18-19).

It would have been *prima facie* obvious at the time of Applicant's invention to modify the invention of Hajirezaei to substitute a sense construct of a PFP cDNA as taught by Tanzer for the antisense construct taught by Hajirezaei. One would have been motivated by the teaching of Hajirezaei that reduction in gene expression and increased sucrose content in plants transformed with an antisense PFP cDNA sequence was generally useful for genetically modifying plants for increased sucrose production. One would have had a reasonable expectation of success because both sense and antisense constructs are effective at inhibiting gene expression in a plant as taught by Tanzer and Hajirezaei. It also would have been *prima facie* obvious at the time of Applicant's

invention to modify the invention of Hajirezaei to substitute the maize ubiquitin promoter taught by Cheng for the CaMV promoter taught by Hajirezaei. The two promoters are strong constitutive promoters and hence are functional equivalents. It would have been obvious to substitute one functional equivalent for another. It further would have been obvious to modify the invention of Hajirezaei to transform sugarcane, rather than tobacco, according to the methods admitted by Applicant to have been known in the art. One would have been motivated to do so because sugarcane is an economically important sugar crop, and hence one would have been motivated to modify sucrose metabolism in sugar cane.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Kim Davis, whose telephone number is (703) 308-0009.

Russell Kallis Ph.D.
July 16, 2002

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600